# Cost-effectiveness of aspirin treatment in the primary prevention of cardiovascular disease events in subgroups based on age, gender, and varying cardiovascular risk

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# Cost-Effectiveness of Aspirin Treatment in the Primary Prevention of Cardiovascular Disease Events in Subgroups Based on Age, Gender, and Varying Cardiovascular Risk

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***Background***—Aspirin is effective for the primary prevention of cardiovascular events, but it remains unclear for which subgroups of individuals aspirin is beneficial. We assessed the cost-effectiveness of aspirin separately for men and women of different ages with various levels of cardiovascular disease risk.

***Methods and Results***—A Markov model was developed to predict the number of cardiovascular events prevented, quality-adjusted life-years, and costs over a 10-year period. Event rates were taken from Dutch population data, and the relative effectiveness of aspirin was taken from a gender-specific meta-analysis. Sensitivity analyses and Monte Carlo simulations were conducted to evaluate the robustness of the results. In 55-year-old persons, aspirin prevented myocardial infarctions in men (127 events per 100 000 person-years) and ischemic strokes in women (17 events per 100 000 person-years). Aspirin implies a net investment and a quality-adjusted life-year gain in men 55 years of age; the incremental cost-effectiveness ratio was 111 949 euros per quality-adjusted life-year (1 euro=$1.27 as of June 2007). Aspirin was cost-effective for 55- and 65-year-old men with moderate cardiovascular risk and men 75 years of age (10-year cardiovascular disease risk >10%). Conversely, aspirin was beneficial for women 65 years of age with high cardiovascular risk and women 75 years of age with moderate cardiovascular risk (10-year cardiovascular disease risk >15%). Results were sensitive to drug treatment costs, effectiveness of aspirin treatment, and utility of taking aspirin.

***Conclusions***—Aspirin treatment for primary prevention is cost-effective for men with a 10-year cardiovascular disease risk of >10% and for women with a risk of >15%. This occurs much later in life for women than men. Therefore, opportunities for the primary prevention of aspirin seem limited in women, and a differentiated preventive strategy seems warranted. **(*Circulation*. 2008;117:2875-2883.)**

**Key Words:** aspirin ■ cardiovascular diseases ■ cost-benefit analysis ■ Markov chains ■ primary prevention

Aspirin is generally prescribed in the secondary prevention of cardiovascular events such as myocardial infarction, stroke, and cardiovascular death.[1] The merits of aspirin in primary prevention strategies are less clear. Meta-analyses of randomized primary prevention trials have indicated that low-dose aspirin (ranging from 100 mg every other day to 500 mg daily) is associated with a reduction in cardiovascular events.[2–5] However, in contrast to this risk reduction, aspirin increases the risk of hemorrhagic stroke and gastrointestinal bleeding even at a low dosage.[6]

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It is difficult to get a clear impression of the risk-to-benefit ratio of aspirin. Reported relative risks or percentages of adverse events in the individual trials or meta-analyses are difficult to trade off directly against cardiovascular events. The range of severity for each type of event varies considerably, as do long-term consequences. Decision analytic modeling offers an appropriate means to combine all relevant outcomes into a familiar and standardized measure: quality-adjusted life-years (QALYs). Previous decision analyses and economic evaluations have shown that the decision of whether to take aspirin as the primary prevention for cardiovascular events depends on the patients' cardiovascular risk level.[7–15]

Recently, a meta-analysis of the role of aspirin in the primary prevention of cardiovascular events revealed important differential effects of aspirin therapy between men and women.[5] Aspirin reduced the risk of myocardial infarction in men and that of ischemic stroke in women. None of the previous decision analyses took these newer, more precise estimates of differential effects of aspirin therapy between the sexes into account.

The aim of this study was to identify subgroups of individuals in whom low-dose aspirin in the primary preven-

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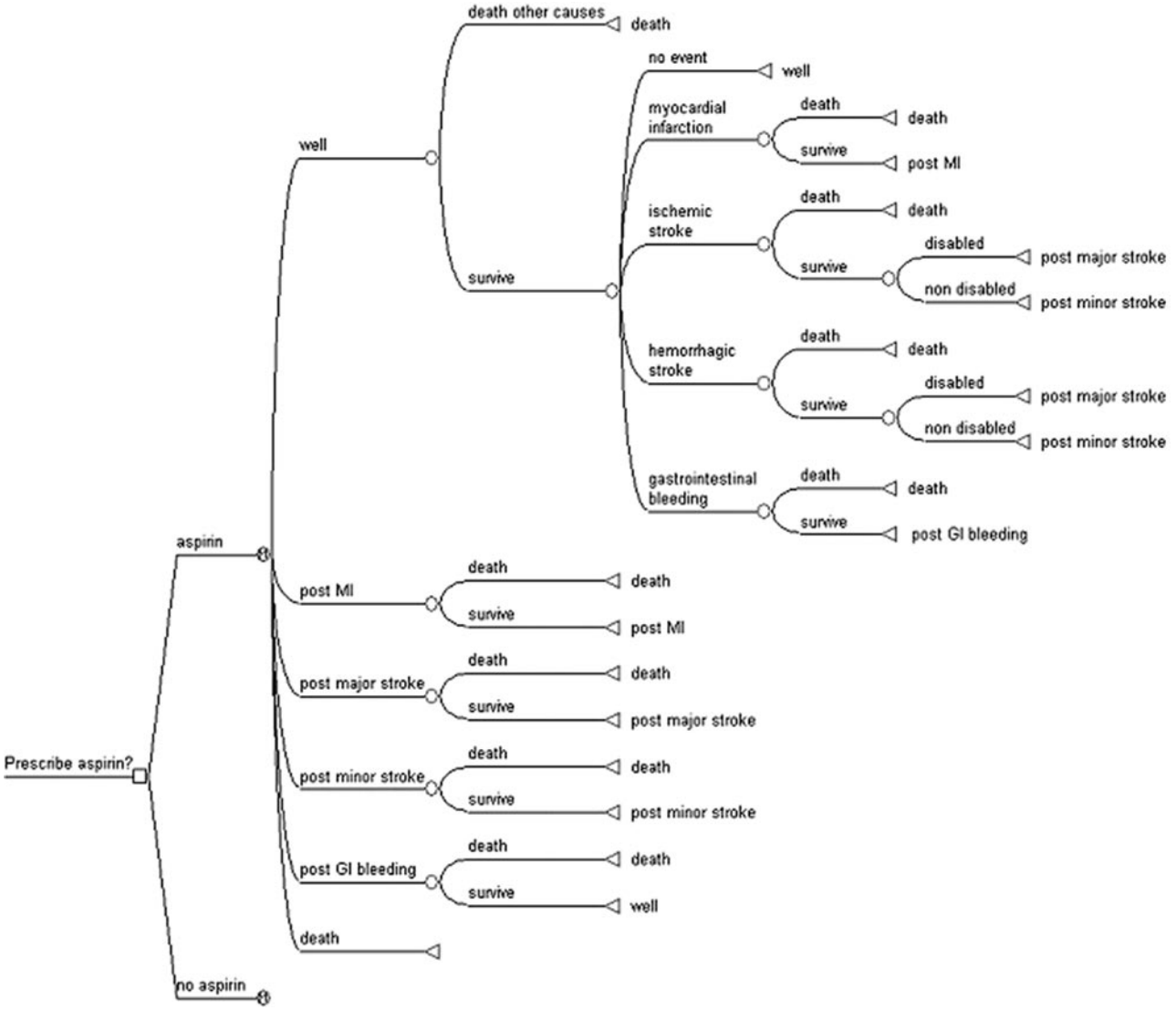


**Figure 1.** Decision tree, including Markov process, for the decision of whether to take aspirin for the primary prevention of cardiovascular events in generally healthy persons. Shown is the generic framework of the model. The tree is fully displayed only for the aspirin treatment arm, but the no aspirin arm has the same detail. The square node at the far left symbolizes the choice between the 2 strategies (aspirin and no aspirin); circles represent chance events. Generally healthy persons cycle through the Markov tree (denoted by a Markov node) and are at risk annually for myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, gastrointestinal bleeding, and death.

tion of cardiovascular disease is beneficial. We developed a decision model to examine the costs and effects of aspirin compared with no treatment in men and women of different ages with various levels of cardiovascular risk.

## Methods

### Model Structure

We developed a Markov model to compare the possible outcomes of the 2 strategies: aspirin and no aspirin.[16] In this model, cycles of 1 year and a total time horizon of 10 years were used. The model was designed to simulate cohorts of initially healthy men or women 45, 55, 65, or 75 years of age without a history of cardiovascular disease. The model consisted of 6 health states: well, post–myocardial infarction, post–major stroke (ischemic or hemorrhagic), post–minor stroke (ischemic or hemorrhagic), post–gastrointestinal bleeding, and death. A graphic presentation of the model is shown in Figure 1. Each individual in the modeled cohort started in the "well" health state. From there, age- and gender-specific probabilities of fatal and nonfatal myocardial infarction, ischemic stroke, hemorrhagic stroke, gastrointestinal bleeding, or dying of another cause determined who made transitions to other health states over time. We did not consider angina pectoris or transient ischemic attacks as separate health states in our model because insufficient data regarding the effectiveness of aspirin on these outcomes were available. In addition, these outcomes are transient health states that may be considered an integral part of survival with cardiovascular disease, ie, without specific long-term consequences.

### Input Parameters

Input parameters, including transition probabilities, treatment effectiveness of aspirin, and utilities, are shown in Table 1. This table lists parameters for a 55-year-old person. Table I of the online Data Supplement lists similar data for persons 45, 65, and 75 years of age. Because the model cycle is 1 year, transition probabilities are reflected by annual incidence rates for the events of interest. We derived incidence estimates of myocardial infarction, ischemic stroke, and hemorrhagic stroke from a record linkage study of

**Table 1. Incidence, Case Fatality, and Overall Mortality Rates for a 55-Year-Old Person and Treatment Effectiveness Data of Aspirin, Utilities, Costs, and Their 95% CIs**

| Parameters | Men | Women | Distribution | Data Source | Reference |
|---|---|---|---|---|---|
| Incidence rates (per 100 000 person-years)* | | | | | |
| Myocardial infarction | 426 (413–440) | 101 (95–108) | Normal | Cohort study | 17 |
| Ischemic stroke | 139 (128–150) | 73 (65–82) | Normal | Cohort study | 18 |
| Hemorrhagic stroke | 31 (26–36) | 19 (15–23) | Normal | Cohort study | 18 |
| Gastrointestinal bleeding | 76 (59–93) | 32 (21–43) | Normal | Cohort study | 19, 20 |
| 1-Year case fatality rate* | | | | | |
| Myocardial infarction | 0.28 (0.26–0.30) | 0.27 (0.23–0.31) | Normal | Cohort study | 21 |
| Ischemic stroke | 0.12 (0.09–0.14) | 0.11 (0.07–0.14) | Normal | Cohort study | 18 |
| Hemorrhagic stroke | 0.44 (0.33–0.56) | 0.45 (0.31–0.60) | Normal | Cohort study | 18 |
| Gastrointestinal bleeding | 0.03 (0.02–0.04) | 0.03 (0.02–0.04) | Normal | Cohort study | 5, 19, 20 |
| Overall 1-year mortality rate (per 100 000 person-years)* | 658 (607–709) | 407 (366–448) | Normal | Actual rates | 22 |
| Treatment effectiveness of aspirin | | | | | |
| Myocardial infarction | 0.68 (0.54–0.86) | 1.01 (0.84–1.21) | Log linear | Meta-analysis | 5 |
| Ischemic stroke | 1.00 (0.72–1.41) | 0.76 (0.63–0.93) | Log linear | Meta-analysis | 5 |
| Hemorrhagic stroke | 1.69 (1.04–2.73) | 1.07 (0.42–2.69) | Log linear | Meta-analysis | 5 |
| Gastrointestinal bleeding† | 1.72 (1.35–2.20) | 1.68 (1.13–2.52) | Log linear | Meta-analysis | 5 |
| Utilities‡ | | | | | |
| Myocardial infarction | 0.88 (0.8–0.95) | | Triangular | Interview | 7, 11, 28 |
| Major stroke§ | 0.5 (0–0.75) | | Triangular | Review | 7, 11, 29, 30 |
| Minor stroke§ | 0.75 (0.6–0.90) | | Triangular | Review | 7, 11, 29, 30 |
| Gastrointestinal bleeding (year 1) | 0.94 (0.88–1.0) | | Triangular | Estimate | 11 |
| Taking aspirin | 0.999 (0.985–1.0) | | Beta | Estimate | 7, 11, 29 |
| Annual cost data, euros‡ | | | | | |
| Aspirin | 97 | | ... | Official tariff | 35, 36 |
| Myocardial infarction | | | | | |
| During first year | 16 570 | | ... | Cost study | 37 |
| During subsequent years | 1007 | | ... | Cost study | 38 |
| Major stroke§ | | | | | |
| During first year | 34 585 | | ... | Cost study | 39 |
| During subsequent years | 20 194 | | ... | Cost study | 39 |
| Minor stroke§ | | | | | |
| During first year | 6064 | | ... | Cost study | 39 |
| During subsequent years | 1038 | | ... | Cost study | 39 |
| Gastrointestinal bleeding (per event) | 1625 | | ... | Estimate | 9 |
| Death | 2579 | | ... | Expert opinion | 39 |

*Risk of events and mortality rates increase with advancing age, except for case fatality rates for gastrointestinal bleeding.
†Risk estimates were derived from the effects of aspirin treatment on major bleeding.
‡Utility and cost estimates mentioned for men are identical for women.
§Both ischemic and hemorrhagic stroke.

routinely collected data on hospital discharges and deaths in the Netherlands by 10-year age groups and gender.[17,18] We calculated age-specific incidence rates using linear interpolation between age groups. We used these rates rather than fixed annual rates in our model because there is an increase in incidence rates with age. Similarly, we derived age- and gender-specific incidence rates of gastrointestinal bleeding and case fatality rates of myocardial infarction, ischemic stroke, and hemorrhagic stroke.[18–21] Specific data on case fatality rates of gastrointestinal bleeding were not available in the literature. The overall risk of dying as a result of gastrointestinal bleeding was estimated at 3% and was varied in the sensitivity analyses. We derived age- and gender-specific annual probabilities of dying from national life tables.[22] These data were used to account for the fact that the cohort in the model ages.

Population-based studies have provided data on risk of death after a first nonfatal stroke or myocardial infarction resulting from fatal recurrent strokes and fatal recurrent cardiac events.[23–26] For survivors of a first stroke or myocardial infarction, the long-term risk of death was approximately twice the risk of dying in the general population of similar gender and age. Using this 2-fold-increased risk and mortality data from life tables, we calculated age-adjusted annual mortality rates for survivors of both nonfatal stroke and myocardial infarction. We assumed that the risk of permanent severe disability after stroke is 33%.[27]

The utilities associated with the different health states also were drawn from the literature and are shown in Table 1.[7,11,28–30] In most cases, they were estimated by time tradeoff techniques described in the original studies.[31] For nonfatal gastrointestinal bleeding that results in only short-term morbidity, a utility of 0.94 was assigned for the 1-year period after the event (ie, 3 weeks deducted from overall survival).[11]

To undertake comparative analyses of the 2 strategies, we applied relative effects of aspirin to the risks for the relevant health events, as indicated by the gender-specific meta-analysis of 6 randomized controlled trials of aspirin for primary prevention.[5] Relative effects of aspirin were assumed to be constant because systematic reviews and meta-analyses suggest that relative risk reductions with aspirin seemed not to vary much across a wide range of underlying risk for cardiovascular disease and were independent of other preventive therapies.[32,33] In addition, we assumed that treatment effectiveness of aspirin in terms of relative risks was constant across all ages because age-specific data were lacking; this assumption is common in cost-effectiveness models.[34]

## Health Outcomes

We determined the expected number of each of the cardiovascular disease events (myocardial infarction, ischemic stroke, and hemorrhagic stroke) and gastrointestinal bleeding, along with differences in life-years and QALYs. QALYs were calculated by multiplying the time a person remained in a certain health state by the utility associated with that particular health state and subsequent summing over all health states. Ten-year cardiovascular disease risk was estimated from the expected number of myocardial infarctions, ischemic strokes, and hemorrhagic strokes in the no aspirin arm divided by the total number of simulated persons.

## Costs

We conducted our economic analysis from the perspective of the healthcare payer. The total drug treatment costs were calculated at 97 euros per person per year. Aspirin drug costs were obtained from the Dutch national drug compendium (19 euros) and increased with the pharmacists' fee (26 euros) and prescription costs of the general practitioner (52 euros) on the assumption that 4 prescriptions were issued each year.[35,36] We distinguished event-related costs and ongoing costs because healthcare costs immediately after an event are higher than in the subsequent years after an event. Event-related costs contained the costs of hospitalization, diagnostic workup, (surgical) intervention, rehabilitation, and nursing home admission during the first year after an event. Ongoing costs reflected the costs of the resource use in the subsequent years after an event. These costs were assigned to a patient for each year that the patient remained in a certain health state. Cost estimates of the event-related costs and ongoing costs were derived from Dutch costs studies, and if these data were not available, we applied European costs estimates or estimated them with the help of experts in the field.[9,37–39] All cost estimates are updated to 2005 with the Dutch inflation indexes (http://statline.cbs.nl) calculated in euros (1 euro=$1.27 as of June 2007) and presented in Table 1.

## Analysis

Life-years, QALYs, and costs were calculated over the 10-year time horizon and are presented as the mean outcomes per patient. Incremental cost-utility ratios were defined as the difference in costs divided by the difference in QALYs. Treatment was considered cost-effective at an incremental cost-utility ratio of 20 000 euros per QALY gained. Sensitivity analyses were performed to evaluate the effect of varying the input parameters over the ranges given in Table 1. Additionally, we evaluated the following scenarios: (1) Lower 95% CI limits were used as relative risk reduction for cardiovascular events; (2) no disutility for taking aspirin was examined; (3) drug treatment costs were limited to costs of aspirin drugs only; and (4) costs were discounted at 4% and benefits at 1.5% and 4% in accordance with current guidelines.[36] Initially, the model also contained secondary events. Because modeling secondary events did not have a large influence on our results, we did not consider events after the first cardiovascular event in our final model. To assess the uncertainty around the modeled output, we performed probabilistic sensitivity analysis using Monte Carlo simulation. We evaluated the clinical courses of 10 000 hypothetical persons for both strategies (aspirin versus no aspirin) 2000 times, with each simulation involving a random draw from each of the input parameter distributions given in Table 1. Multiple outputs were thus calculated, and 95% CIs were derived. Acceptability curves were used to express the uncertainty in the incremental cost-utility ratios from the Monte Carlo simulation. These curves show for each predefined cost-utility ratio (so-called willingness-to-pay threshold) the probability that the cost-utility ratio found in the study is acceptable.[40] The models were developed in TreeAge (version TreeAge Pro Suite 2007, TreeAge Software, Inc, Williamstown, Mass).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

# Results

## Health Outcomes

The number and type of events for 10 000 men and women 55 years of age without a history of cardiovascular disease in both treatment groups estimated by using the Markov model are presented in Table 2. Aspirin treatment yielded the greatest reduction in myocardial infarctions in men (127 events per 100 000 person-years) and a small reduction of ischemic strokes in women (17 events per 100 000 person-years). For a hypothetical 55-year-old man with no additional risk factors, aspirin treatment resulted in a slightly increased life expectancy (from 9.67 to 9.69 years) and increased QALYs (from 9.63 to 9.64) over 10 years (Table 2). Increasing cardiovascular risk to 5 times the baseline risk resulted in a considerably higher QALY gain for aspirin treatment (Table 3). Conversely, for a hypothetical 55-year-old woman with no additional risk factors, there appears to be no QALY gain with aspirin treatment. For women, the expected number of prevented ischemic events was too small to outweigh the increase in hemorrhagic stroke and gastrointestinal bleeding. Aspirin treatment resulted in only a very small QALY gain even when cardiovascular risk was increased 5 times the baseline risk (Table 4).

## Costs and Incremental Cost-Utility Ratios

Substantial differences in costs were observed between men and women. Median total costs per person for the 10-year follow-up of a 55-year-old person were about 1350 euros for men and 600 euros for women. Aspirin treatment was more expensive, costing 2150 euros for men and 1450 euros for women (Table 2). For a 55-year-old man with no additional risk factors, aspirin was more effective and more expensive than no treatment. The incremental cost-utility ratio of aspirin treatment compared with no treatment was 111 949 euros per QALY gained (Table 3). The incremental cost-utility ratio of aspirin improved as the risk of cardiovascular events increased. For a 55-year-old man with a 2-times-increased cardiovascular risk, aspirin treatment resulted in an incremental cost-utility ratio of 20 298 euros per QALY gained compared with no treatment. With 20 000 euros used as a threshold for cost-effectiveness, treatment with aspirin was also cost-effective for men 65 and 75 years of age regardless of the number of risk factors present (Table 3).

**Table 2. Simulated Outcomes (Mean of 2000 Simulations) of Effectiveness and Costs of Aspirin Compared With No Aspirin on Cohorts of 10 000 Dutch Men or Women 55 Years of Age at Baseline Followed Up for 10 Years**

| | Men | | Women | |
|---|---|---|---|---|
| | Aspirin | No Aspirin | Aspirin | No Aspirin |
| Myocardial infarction, n | 275 (243–307) | 402 (365–441) | 99 (80–119) | 98 (78–117) |
| Ischemic stroke, n | 131 (109–154) | 131 (109–153) | 54 (41–68) | 71 (55–88) |
| Hemorrhagic stroke, n | 50 (37–64) | 29 (19–41) | 20 (12–29) | 19 (11–28) |
| Major gastrointestinal bleeding, n | 124 (103–144) | 72 (57–89) | 52 (39–66) | 31 (21–42) |
| Fatal myocardial infarction, n | 88 (64–113) | 130 (101–159) | 29 (17–43) | 29 (18–43) |
| Fatal ischemic stroke, n | 22 (9–39) | 22 (9–38) | 8 (2–17) | 10 (3–20) |
| Fatal hemorrhagic stroke, n | 24 (13–37) | 14 (6–26) | 9 (4–18) | 9 (3–17) |
| Fatal major gastrointestinal bleeding, n | 4 (1–11) | 3 (0–7) | 2 (0–5) | 1 (0–4) |
| Life expectancy, y | 9.687 (9.657–9.715) | 9.673 (9.643–9.701) | 9.798 (9.775–9.821) | 9.798 (9.775–9.820) |
| QALY expectancy, y | 9.641 (9.612–9.668) | 9.634 (9.606–9.661) | 9.774 (9.751–9.797) | 9.781 (9.758–9.804) |
| Costs per person, euros | 2158 (1974–2340) | 1358 (1191–1537) | 1471 (1362–1594) | 581 (457–712) |

Numbers are point estimates (95% CIs).

For most women, aspirin treatment resulted in increased costs and worse health outcomes. However, women 65 years of age with a 5-times-increased cardiovascular risk aspirin tended to have favorable health outcomes against higher costs compared with no treatment. The incremental cost-utility ratio of aspirin treatment compared with no treatment was 5747 euros per QALY gained. Treatment with aspirin also was cost-effective for women 75 years of age with a 2-times-increased cardiovascular risk but was not cost-effective for women of the same age without increased cardiovascular risk

**Table 3. Estimated 10-Year Cardiovascular Risk, Life Expectancy, and Costs of Aspirin Compared With No Aspirin on Cohorts of 10 000 Dutch Men at Different Ages Over a 10-Year Period**

| Cohort | 10-Year CVD Risk, %* | Life-Years for Aspirin | Life-Years for No Aspirin | Difference in Life-Years, d (95% CI) | QALYs for Aspirin | QALYs for No Aspirin | Difference in QALYs, d (95% CI) | Costs for Aspirin, euros | Costs for No Aspirin, euros | Difference in Costs, euros (95% CI) | ICER, euros/QALY |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 45-Year-old men | | | | | | | | | | | |
| No risk factors | 2 | 9.891 | 9.886 | 2 (0–4) | 9.865 | 9.869 | −1 (−3–0) | 1483 | 588 | 896 (798–993) | NA |
| 2× Increased CVD risk | 5 | 9.874 | 9.862 | 4 (2–6) | 9.835 | 9.830 | 2 (0–5) | 1884 | 1074 | 810 (640–976) | 141 160 |
| 5× Increased CVD risk | 11 | 9.825 | 9.794 | 11 (8–15) | 9.748 | 9.716 | 12 (8–16) | 3056 | 2498 | 558 (263–853) | 17 408 |
| 55-Year-old men | | | | | | | | | | | |
| No risk factors | 6 | 9.687 | 9.673 | 5 (2–8) | 9.641 | 9.634 | 3 (0–5) | 2158 | 1358 | 801 (649–955) | 111 949 |
| 2× Increased CVD risk | 11 | 9.638 | 9.607 | 12 (8–15) | 9.563 | 9.532 | 11 (7–15) | 3075 | 2458 | 618 (368–858) | 20 298 |
| 5× Increased CVD risk | 24 | 9.499 | 9.418 | 30 (24–36) | 9.340 | 9.247 | 34 (28–40) | 5643 | 5481 | 162 (−244–574) | 1753 |
| 65-Year-old men | | | | | | | | | | | |
| No risk factors | 11 | 9.072 | 9.041 | 11 (7–15) | 8.998 | 8.973 | 9 (5–13) | 3272 | 2549 | 722 (543–904) | 29 483 |
| 2× Increased CVD risk | 19 | 8.944 | 8.871 | 26 (21–32) | 8.818 | 8.746 | 26 (21–32) | 4855 | 4382 | 473 (165–778) | 6570 |
| 5× Increased CVD risk | 41 | 8.594 | 8.420 | 64 (56–72) | 8.328 | 8.141 | 68 (59–76) | 9072 | 9066 | 6 (−490–491) | 34 |
| 75-Year-old men | | | | | | | | | | | |
| No risk factors | 17 | 7.617 | 7.569 | 18 (12–23) | 7.529 | 7.489 | 15 (9–20) | 4298 | 3647 | 651 (489–815) | 16 279 |
| 2× Increased CVD risk | 30 | 7.317 | 7.187 | 47 (40–55) | 7.173 | 7.046 | 46 (40–53) | 6126 | 5700 | 427 (155–684) | 3374 |
| 5× Increased CVD risk | 56 | 6.558 | 6.263 | 108 (97–118) | 6.277 | 5.980 | 108 (99–119) | 10 465 | 10 298 | 167 (−291–604) | 562 |

CVD indicates cardiovascular disease; ICER, incremental cost-utility ratio.

*The 10-year cardiovascular disease risk was estimated from the expected number of myocardial infarctions, ischemic strokes, and hemorrhagic strokes in the no aspirin arm divided by the total number of simulated persons.

**Table 4. Estimated 10-Year Cardiovascular Risk, Life Expectancy and Costs of Aspirin Compared With No Aspirin On Cohorts of 10 000 Dutch Women at Different Ages Over a Ten-year Period**

| Cohort | 10-Year CVD Risk, %* | Life-Years for Aspirin | Life-Years for No Aspirin | Difference in Life-Years, d (95% CI) | QALYs for Aspirin | QALYs for No Aspirin | Difference in QALYs, d (95% CI) | Costs for Aspirin, euros | Costs for No Aspirin, euros | Difference in Costs, in euros (95% CI) | ICER, euros/QALY |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 45-Year-old women | | | | | | | | | | | |
| No risk factors | 1 | 9.910 | 9.910 | 0 (−1–1) | 9.892 | 9.901 | −3 (−4–−2) | 1241 | 313 | 928 (858–989) | NA |
| 2× Increased CVD risk | 2 | 9.903 | 9.903 | 0 (−1–1) | 9.878 | 9.885 | −3 (−4–−1) | 1434 | 546 | 889 (815–954) | NA |
| 5× Increased CVD risk | 4 | 9.880 | 9.879 | 0 (−1–2) | 9.836 | 9.838 | −1 (−2–1) | 2011 | 1232 | 779 (667–872) | NA |
| 55-Year-old women | | | | | | | | | | | |
| No risk factors | 2 | 9.798 | 9.798 | 0 (−2–2) | 9.774 | 9.782 | −3 (−4–−1) | 1471 | 581 | 890 (808–968) | NA |
| 2× Increased CVD risk | 4 | 9.782 | 9.781 | 0 (−1–2) | 9.745 | 9.749 | −1 (−3–0) | 1837 | 1015 | 822 (730–909) | NA |
| 5× Increased CVD risk | 8 | 9.732 | 9.728 | 1 (−1–3) | 9.660 | 9.655 | 2 (0–4) | 2909 | 2281 | 628 (488–765) | 114 356 |
| 65-Year-old women | | | | | | | | | | | |
| No risk factors | 5 | 9.507 | 9.505 | 1 (−2–4) | 9.467 | 9.469 | −1 (−3–2) | 2118 | 1340 | 778 (661–897) | NA |
| 2× Increased CVD risk | 9 | 9.439 | 9.433 | 2 (−1–5) | 9.369 | 9.362 | 3 (0–6) | 2951 | 2331 | 620 (470–758) | 85 467 |
| 5× Increased CVD risk | 21 | 9.240 | 9.225 | 5 (2–9) | 9.095 | 9.063 | 12 (8–16) | 5284 | 5099 | 185 (−37–377) | 5747 |
| 75-Year-old women | | | | | | | | | | | |
| No risk factors | 12 | 8.683 | 8.669 | 5 (0–10) | 8.617 | 8.601 | 6 (1–10) | 3194 | 2644 | 550 (393–701) | 34 173 |
| 2× Increased CVD risk | 21 | 8.449 | 8.418 | 11 (6–16) | 8.340 | 8.296 | 16 (11–21) | 4645 | 4396 | 249 (56–421) | 5791 |
| 5× Increased CVD risk | 44 | 7.825 | 7.759 | 24 (18–31) | 7.594 | 7.490 | 38 (32–45) | 8383 | 8849 | −466 (−749–−214) | −4465 |

Abbreviations as in Table 3.

*The 10-year cardiovascular disease risk was estimated from the expected number of myocardial infarctions, ischemic strokes, and hemorrhagic strokes in the no aspirin arm divided by the total number of simulated persons.

(Table 4). Aspirin treatment was cost-effective for men with a 10-year cardiovascular disease risk >10% and for women when the risk was >15%.

Figure 2 presents the acceptability curves for cost-utility ratios for aspirin treatment compared with no treatment for 55-year-old men with various levels of cardiovascular risk. The probability that cardiovascular disease prevention with aspirin therapy is cost-effective increases with an increasing threshold for the incremental cost-utility; the estimated likelihood of a cost-utility ratio falling below the Dutch threshold of 20 000 euros per QALY gained for a 55-year-old man with no additional risk factors was 0, but the probability would increase to 25% if the willingness-to-pay threshold was increased to 80 000 euros per QALY gained, as recently proposed by the Dutch Council for Public Health and Health Care.[41] The curve for 55-year-old men with a 5-times-increased cardiovas-

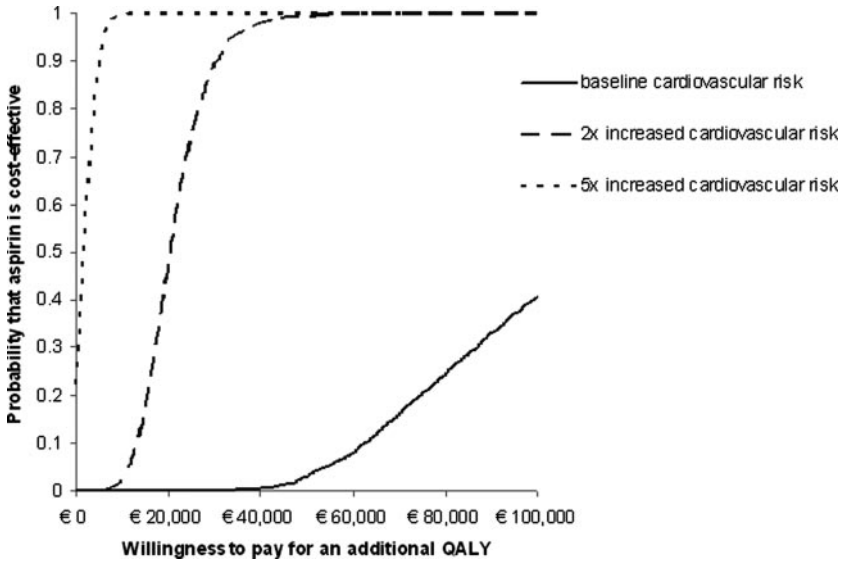


**Figure 2.** Acceptability curves for aspirin based on multiple simulated incremental cost-utility ratios for 55-year-old men with increasing risks for cardiovascular disease. The *x* axis shows a range of values that society may be willing to pay for health benefits, and the elevation of the curve (on the *y* axis) denotes the probability that aspirin has a incremental cost-utility ratio that is more favorable than the corresponding willingness to pay. The baseline risk for 55-year-old men without a history of cardiovascular disease corresponds to a 10-year cardiovascular disease risk of 6%, a 2-times-increased cardiovascular risk to 11%, and a 5-times-increased vascular risk to 24%.

**Table 5. Sensitivity Analyses**

| | Difference in QALYs, d | Incremental Cost-Utility Ratio, euros/QALY |
|---|---|---|
| Base-case analysis* | 3 | 111 949 |
| Relative effectiveness estimates | | |
| Myocardial infarction: 0.54 | 6 | 40 375 |
| Ischemic stroke: 0.72 | 5 | 44 022 |
| Hemorrhagic stroke: 1.04 | 5 | 56 165 |
| Utilities | | |
| Taking aspirin: 1 | 6 | 47 630 |
| Drug costs | | |
| Costs of aspirin drugs only: 19 euros | 3 | 6474 |
| Discount rate | | |
| Costs, 4%; benefits, 4% | 2 | 133 853 |
| Costs, 4%; benefits, 1.5% | 2 | 107 098 |

*Base-case analysis for 55-year-old men with no additional risk factors.

cular risk shows a 95% probability that aspirin is cost-effective at a willingness-to-pay threshold of 6000 euros per QALY gained. For women with a 5-times-increased cardiovascular risk, the probability that aspirin had a cost per QALY gained <80 000 euros was estimated at 25%.

### Sensitivity Analyses

The results of the cost-utility analysis were sensitive to drug treatment costs, treatment effectiveness, and utility of taking aspirin (Table 5). When drug treatment costs were reduced to costs of aspirin drugs only, the incremental cost-utility ratio of aspirin treatment compared with no treatment decreased from 111 949 to 6474 euros per QALY gained for 55-year-old men with no additional risk factors. When the lower limit of the 95% CI of the relative risk reduction for cardiovascular events was used, the QALY gain was doubled compared with the base case. Assuming no disutility from taking medication daily also made aspirin twice as (cost-) effective as the base case. The model results were robust for different discount scenarios and ranges of other utilities and input parameters as shown in Table 1.

## Discussion

Our analyses indicate that aspirin treatment for the primary prevention of cardiovascular disease is cost-effective once cardiovascular risk surpasses a certain threshold. Using the threshold of 20 000 euros per QALY, aspirin was cost-effective for men with a 10-year cardiovascular disease risk >10% and for women when the risk was >15%. In general, this occurs much later in life for women than men. Treatment with aspirin was cost-effective for men 75 years of age regardless of the number of risk factors present and for 55- and 65-year-old men with ≥2 cardiovascular risk factors (eg, diabetes mellitus, hypertension, hyperlipidemia, or cigarette smoking). It also was cost-effective for women 75 years of age with a 2-times-increased cardiovascular risk and women 65 years of age with 5-times-increased risk.

A gender-specific meta-analysis of >50 000 women and 40 000 men enrolled in 6 randomized controlled trials of low-dose aspirin in the primary prevention of cardiovascular events demonstrated that aspirin reduced the risk of overall cardiovascular events but increased the risk of hemorrhagic stroke and gastrointestinal bleeding in both sexes.[5] It also reduced the risk of myocardial infarction (but not stroke) in men and ischemic stroke (but not myocardial infarction) in women. Despite controversies that exist about the differences in cardioprotection observed between the sexes,[42] we used those relative risks to identify the specific subgroups for whom the balance of benefits and harms is most favorable for aspirin.

In the past decade, several decision analyses and economic evaluations attempted to balance the benefits and harms of aspirin therapy.[7–15] A decision analysis reported that routine use of low-dose aspirin is as likely to be associated with benefit as harm, but that analysis was limited to elderly people without cardiovascular disease.[8] Previous cost-effectiveness analyses that examined the threshold to recommend aspirin reported that its use was warranted from a 10-year cardiovascular disease risk that varied between 7.5% and 15%.[9,11,12,14,15] Our model generally confirmed those results. In contrast to those earlier studies, we included recent evidence about differential effects of aspirin therapy between men and women in our decision model. Furthermore, we distinguished between ischemic and hemorrhagic stroke. In addition, we predicted the benefits in life expectancy, quality-adjusted life expectancy, and costs of aspirin prevention in a wide range of subgroups, ie, in men and women of different ages with various levels of cardiovascular disease. Consequently, our study provides more complete estimates of the (cost-)effectiveness of the use of aspirin for the primary prevention of cardiovascular disease. These analyses provide physicians or decision makers with quantitative information on the merits of a preventive strategy. This information may be used to decide whether it would be cost-effective to prescribe aspirin for a person with a particular risk profile.

Our model has certain limitations. We did not model patients with particular cardiovascular risk factors such as diabetes, hypertension, or smoking because relative risks associated with aspirin in subgroups of patients with coronary risk factors were, unfortunately, not available in the literature. Therefore, the risk of adverse effects such as hemorrhagic stroke resulting from uncontrolled blood pressure could not be accounted for. The benefits and cost-effectiveness of aspirin for patients with high blood pressure may be less favorable. The simulations were run for 10 years instead of the complete lifetime. However, 10-year risk estimates are used commonly in risk prediction charts for cardiovascular disease prevention.[43,44] Moreover, we considered this period long enough to capture the major health and economic consequences of taking aspirin in the primary prevention of cardiovascular events. Our results are based on a model that did not incorporate the detailed course of persons after their initial event. Instead, an increased mortality rate was applied after the onset of a first cardiovascular event, and an average disability weight was applied to all survivors. This simplified approach was adopted because modeling secondary events

did not have a large influence on our results, and it prevented the model from becoming too complex. Another limitation is that an individual cannot be simulated to experience >1 event in a year because the model operates in discrete 1-year intervals. However, because secondary cardiovascular events were not considered, the only shortcoming may be that a first-ever cardiovascular event cannot occur within the same cycle as gastrointestinal complications or vice versa. The probability that those 2 events for an individual occur concomitantly, however, is very small. Other model limitations were evaluated by changing input parameters in sensitivity analyses. With regard to drug treatment costs, it appeared that costs of visiting a physician and pharmacist were important costs to take into account. The incremental cost-utility ratio of aspirin treatment compared with no treatment reduced considerably under an aspirin drug cost-only scenario. Given that aspirin is easily available over the counter and at a relatively low price, the possibility of self-medication may be considered. Self-medication of aspirin would save individuals the time of consulting a general practitioner and pharmacist and would reduce the financial burden of drug treatment from the National Health Service. However, it may not be realistic to expect that persons are willing to buy aspirin for preventing a cardiovascular event themselves. The uncertainty of cost estimates was not considered in our Monte Carlo simulations. Therefore, the uncertainty in our model outcomes resulted only from uncertainty in probability parameters, treatment effectiveness of aspirin, and utilities associated with each health state. If the uncertainty around cost estimates had been taken into account, it would have resulted in wider CIs for costs.

US costs estimates may be different from Dutch cost estimates. However, a more or less global increase in costs, in accordance with differences between US and Dutch cost estimates, is unlikely to change the overall conclusions. In fact, the incremental cost-effectiveness ratios would probably be even higher, and these higher ratios would strengthen our conclusion that aspirin is cost-effective only in persons at higher cardiovascular risk. Furthermore, Dutch physicians (and primary care physicians in other Western European countries) generally know their own patients with vascular risk factors reasonably well. In primary care settings in the United States, however, the situation may be different, and screening costs to identify patients at risk should be taken into account. Finally, we did not include costs for comedication in our baseline economic analysis because costs for comedication will be similar for both strategies (aspirin versus no aspirin) and therefore the incremental costs will not be different.

Our results also were sensitive to variations in treatment efficacy estimates and the utility of taking aspirin, which has been reported previously.[7,11,14] Because a modest disutility of taking aspirin had important effects on the effectiveness of aspirin, more research is necessary to determine what tradeoffs people are willing to make for routine preventive care. We did not model incomplete adherence for taking aspirin, although we used efficacy estimates that came from trials that used intention-to-treat analyses and therefore incorporated some of the effects of incomplete adherence.

Recently, it was debated whether physicians have gone too far with preventive medicine and overresponded to low levels of risk.[45] Primary prevention that is too aggressive might lead to medicalization of life and turning many healthy people into worried patients by prescribing drugs for what would previously have been considered normal and healthy states.

## Conclusions

This analysis demonstrated that aspirin treatment for primary prevention is cost-effective for men with a 10-year cardiovascular disease risk >10% and for women when the risk was >15%. In general, this occurs much later in life for women than men. Therefore, opportunities for the primary prevention of aspirin seem limited in women, and a gender-differentiated preventive strategy seems warranted.

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## Disclosures

None.

## References

1. Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
2. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart*. 2001;85:265–271.
3. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2002;136:161–172.
4. Eidelman RS, Hebert PR, Weisman SM, Hennekens CH. An update on aspirin in the primary prevention of cardiovascular disease. *Arch Intern Med*. 2003;163:2006–2010.
5. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA*. 2006;295:306–313.
6. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study, 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143:1–13.
7. Augustovski FA, Cantor SB, Thach CT, Spann SJ. Aspirin for primary prevention of cardiovascular events. *J Gen Intern Med*. 1998;13:824–835.
8. Nelson MR, Liew D, Bertram M, Vos T. Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged > or =70. *BMJ*. 2005;330:1306.
9. Lamotte M, Annemans L, Evers T, Kubin M. A multi-country economic evaluation of low-dose aspirin in the primary prevention of cardiovascular disease. *Pharmacoeconomics*. 2006;24:155–169.
10. Marshall T. The cost-effectiveness of drug treatments for primary prevention of cardiovascular disease: a modelling study. *Eur J Cardiovasc Prev Rehabil*. 2006;13:523–528.
11. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. *Ann Intern Med*. 2006;144:326–336.
12. Annemans L, Lamotte M, Kubin M, Evers T, Verheugt FW. Which patients should receive aspirin for primary prevention of cardiovascular disease? An economic evaluation. *Int J Clin Pract*. 2006;60:1129–1137.

13. Franco OH, der Kinderen AJ, De Laet C, Peeters A, Bonneux L. Primary prevention of cardiovascular disease: cost-effectiveness comparison. *Int J Technol Assess Health Care*. 2007;23:71–79.
14. Pignone M, Earnshaw S, Pletcher MJ, Tice JA. Aspirin for the primary prevention of cardiovascular disease in women. *Arch Intern Med*. 2007; 167:290–295.
15. Tsutani K, Igarashi A, Fujikawa K, Evers T, Kubin M, Lamotte M, Annemans L. A health economic evaluation of aspirin in the primary prevention of cardiovascular disease in Japan. *Intern Med*. 2007;46: 157–162.
16. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13:322–338.
17. Koek HL, de Bruin A, Gast A, Gevers E, Kardaun JW, Reitsma JB, Grobbee DE, Bots ML. Incidence of first acute myocardial infarction in the Netherlands. *Neth J Med*. 2007;65:434–441.
18. Jager-Geurts MH, Peters RJ, van Dis SJ, Bots ML. Cardiovascular diseases in the Netherlands 2006: figures on risk factors, morbidity and mortality. The Hague, The Netherlands: Netherlands Heart Foundation; 2006. Available at: http://www.hartstichting.nl. Accessed August 20, 2007.
19. van Leerdam ME, Vreeburg EM, Rauws EA, Geraedts AA, Tijssen JG, Reitsma JB, Tytgat GN. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. *Am J Gastroenterol*. 2003;98:1494–1499.
20. Rockall TA, Logan RF, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom: Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. *BMJ*. 1995;311:222–226.
21. Koek HL, de Bruin A, Gast F, Gevers E, Kardaun JW, Reitsma JB, Grobbee DE, Bots ML. Short- and long-term prognosis after acute myocardial infarction in men versus women. *Am J Cardiol*. 2006;98:993–999.
22. Statistics Netherlands (CBS). Lifetables Dutch population by age and sex, 1996–2000. Voorburg/Heerlen, the Netherlands: Statistics Netherlands; 2002. Available at: http://statline.cbs.nl. Accessed March 16, 2006.
23. Brønnum-Hansen H, Davidsen M, Thorvaldsen P. Long-term survival and causes of death after stroke. *Stroke*. 2001;32:2131–2136.
24. Fogelholm R, Murros K, Rissanen A, Avikainen S. Long term survival after primary intracerebral haemorrhage: a retrospective population based study. *J Neurol Neurosurg Psychiatry*. 2005;76:1534–1538.
25. Brønnum-Hansen H, Jørgensen T, Davidsen M, Madsen M, Osler M, Gerdes LU, Schroll M. Survival and cause of death after myocardial infarction: the Danish MONICA study. *J Clin Epidemiol*. 2001;54: 1244–1250.
26. Bergman L, van der Meulen JH, Limburg M, Habbema JD. Costs of medical care after first-ever stroke in the Netherlands. *Stroke*. 1995;26: 1830–1836.
27. Wolfe CD. The impact of stroke. *Br Med Bull*. 2000;56:275–286.
28. Tsevat J, Goldman L, Soukup JR, Lamas GA, Connors KF, Chapin CC, Lee TH. Stability of time-tradeoff utilities in survivors of myocardial infarction. *Med Decis Making*. 1993;13:161–165.
29. Naglie IG, Detsky AS. Treatment of chronic nonvalvular atrial fibrillation in the elderly: a decision analysis. *Med Decis Making*. 1992;12:239–249.
30. Post PN, Stiggelbout AM, Wakker PP. The utility of health states after stroke: a systematic review of the literature. *Stroke*. 2001;32:1425–1429.
31. Torrance GW, Thomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. *Health Serv Res*. 1972;7:118–133.
32. Bartolucci AA, Howard G. Meta-analysis of data from the six primary prevention trials of cardiovascular events using aspirin. *Am J Cardiol*. 2006;98:746–750.
33. Hennekes CH, Sacks FM, Tonkin A, Jukema JW, Byington RP, Pitt B, Berry DA, Berry SM, Ford NF, Walker AJ, Natarajan K, Sheng-Lin C, Fiedorek FT, Belder R. Additive benefits of pravastatin and aspirin to decrease risks of cardiovascular disease: randomized and observational comparisons of secondary prevention trials and their meta-analyses. *Arch Intern Med*. 2004;164:40–44.
34. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the Economic Evaluation of Health Care Programmes*. New York, NY: Oxford University Press Inc; 2005.
35. van Loenen A. *Pharmacotherapeutic Compass 2005*. Amstelveen, the Netherlands: Health Care Insurance Board; 2005.
36. Oostenbrink JB, Bouwmans CA, Koopmanschap MA, Rutten FF. *Instructions for Cost Assessment, Methods and Directive of Prices for Economic Evaluation in Health Care* [in Dutch]. Amstelveen, the Netherlands: Health Care Insurance Board; 2004.
37. de Boer MJ, van Hout BA, Liem AL, Suryapranata H, Hoorntje JC, Zijlstra F. A cost-effective analysis of primary coronary angioplasty versus thrombolysis for acute myocardial infarction. *Am J Cardiol*. 1995; 76:830–833.
38. Johannesson M, Jonsson B, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease: Scandinavian Simvastatin Survival Study Group. *N Engl J Med*. 1997;336:332–336.
39. Buskens E, Nederkoorn PJ, Buijs-van der Woude T, Mali WP, Kappelle LJ, Eikelboom BC, van der Graaf Y, Hunink MG. Imaging of carotid arteries in symptomatic patients: cost-effectiveness of diagnostic strategies. *Radiology*. 2004;233:101–112.
40. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ*. 1994;3:309–319.
41. *Sensible and Sustainable Care*. Zoetermeer, the Netherlands; Council for Public Health and Health Care: 2006.
42. Ridker PM, Cook NR, Buring JE. Use of aspirin as primary prevention of cardiovascular events. *JAMA*. 2006;296:391–392.
43. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J*. 1991;121:293–298.
44. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM, for the SCORE Project Group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003.
45. Christie B. Guidelines on treating risk factors turn healthy people into patients, doctors say. *BMJ*. 2006;333:988.

## CLINICAL PERSPECTIVE

Aspirin is effective for the primary prevention of cardiovascular events, but it remains unclear for which subgroups of individuals aspirin is beneficial. We assessed the cost-effectiveness of aspirin separately for men and women of different ages with various levels of cardiovascular disease risk. Our analyses demonstrated that aspirin treatment for the primary prevention of cardiovascular disease was cost-effective for men with a 10-year cardiovascular disease risk $>10\%$ and for women when the risk was $>15\%$. In general, this occurs much later in life for women than men. Treatment with aspirin was cost-effective for men 75 years of age regardless of the number of risk factors present and for 55- and 65-year-old men with $\geq 2$ cardiovascular risk factors (such as diabetes mellitus, hypertension, hyperlipidemia, or cigarette smoking). For most women, aspirin treatment resulted in increased costs and worse health outcomes. However, aspirin was cost-effective for women 65 years of age with high cardiovascular risk and women 75 years of age with moderate cardiovascular risk. Therefore, opportunities for primary prevention of aspirin seem limited in women, and a gender-differentiated preventive strategy seems warranted.